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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,324	07/13/2001	Shizuo Akira	31671-173143	2302

26694 7590 01/14/2003

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EXAMINER

QIAN, CELINE X

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 01/14/2003

8

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/889,324	AKIRA ET AL.	
	Examiner Celine X Qian	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 29 October 2002.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-51 is/are pending in the application.
- 4a) Of the above claim(s) 8,9 and 12-51 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-7,10 and 11 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|--|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ . |
| 2) <input checked="" type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>5</u> . | 6) <input type="checkbox"/> Other: _____ . |

DETAILED ACTION

Claims 1-51 are pending in the application.

Election/Restrictions

Applicant's election without traverse of Group I in Paper No. 7 is acknowledged.

Accordingly, claims 8, 9, 12-51 are withdrawn from consideration for being directed to non-elected subject matter. Claims 1-7, 10 and 11 are currently under examination.

Drawings

The drawings are objected to because of the informalities as indicated by Draftsperson on PTO form 948 (see attached form). A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance. Any response to this office action which does not response to the above objections will be considered non-responsive.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 10 and 11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

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convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description requirement is set forth by 35 U.S.C. 112, first paragraph which states that the: “*specification* shall contain a written description of the invention. . .[emphasis added].” The written description requirement has been well established and characterized in the case law. A specification must convey to one of skill in the art that “as of the filing date sought, [the inventor] was in possession of the invention.” See *Vas Cath v. Mahurkar* 935 F.2d 1555, 1560 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Applicant may show that he is in “possession” of the invention claimed by describing the invention with all of its claimed limitations “by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention.” See *Lockwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

The claims encompass a model non-human animal being unresponsive to bacterial cell components. In analyzing whether the written description requirement is met, it is first determined whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. The specification discloses three knockout mice, MyD88-/-, TLR2-/- and TLR4-/-, that are unresponsive to bacterial cell components. However, no other animal models unresponsive to bacterial cell components are disclosed. The art teaches mouse harboring mutation in TLR4 is unresponsive to lipopolysaccharide of bacterial cells. The specification describes only one species of the animal that is unresponsive to bacterial cell components. With limited information disclosed in the

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specification, an artisan would have not been able to predict whether mutation or deletion of the same genes in other non-human animal would result in the same phenotype compared to the disclosed knockout mice or mice harboring mutation in TLR4 gene. As such, the specification fails to describe a representative number of bacterial cell component unresponsive non-human animals by their complete structure or other relevant characteristic. Therefore, the specification does not describe the invention in such a way to convey one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed.

Claims 1-7, 10 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mouse comprising homozygous disruption of TLR4, TLR2 or MyD88 in its genome and exhibiting the phenotype of unresponsive to bacterial cell components, does not reasonably provide enablement for any other non-human animal comprising disruption of these genes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the relative skill of those in the art; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue" (MPEP 2164.01 (a)).

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The nature of the invention is a transgenic non-human animal whose genome comprises a disruption in its endogenous MyD88, TLR2 or TLR4 gene, and said animal having decreased level or no MyD88, TLR2 or TLR4 protein, or mutated MyD88, TLR2 or TLR4 protein and is unresponsive to bacterial cell component.

The breadth of claims is very broad. In the instant case, the claims are drawn to a transgenic non-human animal containing a disrupted endogenous MyD88, TLR2 or TLR4 gene with decreased or no expression of the wild type protein and unresponsive to bacterial cell components. The claims encompass any transgenic non-human animal containing any type of mutation or disruption in MyD88, TLR2 or TLR4 gene.

The amount of guidance and working example in the specification is limited. The specification does not provide an enabling disclosure to make a non-human animal unresponsive to bacterial cell components except knockout mice with MyD88, TLR2 or TLR4 gene disruption. The specification fails to teach how to make other non-human animals unresponsive to bacterial cell components. Without teaching from the specification, one skilled in the art would have to turn to prior art for guidance to make and use the transgenic animal as claimed.

State of the Art, Predictability or Unpredictability of the art, Amount of experimentation necessary and Skill level of the artisan: The specification fails to provide an enabling disclosure for the generation of other species of animals that are unresponsive to bacterial cell components besides mice having a disruption in the MyD88, TLR2 or TLR4 gene because the guidance offered in the specification is limited to the generation of mice harboring such mutations and no teachings or guidance are offered with regard to how one would generate any other type of animal. Since homologous recombination is required for gene targeting methods such as

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employed in the instant invention, embryonic stem (ES) cell must be available to carry out the method. The only species in which the ES is available is the mouse (see e.g. Bradley et al., paragraph bridging pages 537-538). Campbell and Wilmut, 1997 acknowledge reports of ES-like cell lines in a number of species, but emphasize that as yet there are no reports of any cell lines which contribute to the germ line in any species other than the mouse (p.65). Likewise, Mullins et al. (1996, Clin. Invest. Vol 97, no. 7, 1557-1560) teach that “although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated. This remains a major goal for the future and may well require the use of novel strategies which depart widely from the traditional methods used in the mouse” (p.1558, column 2, paragraph 1). Therefore, no knockout animals can be made for any species other than the mouse at the time of filing. As such, the invention while being enabled for a homozygous knockout mouse, generated by using ES cells, containing homozygous disruption for the MyD88, TLR2 or TLR4 gene with disclosed phenotype, does not enable the generation of other non-human animals unresponsive to bacterial cell components.

In view of the limited guidance in the specification and the unpredictability of the art, one skilled in the art would have to engage in undue amount of experimentation overcome the problems as discussed above. Therefore, the invention is not enabled as claimed.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 1-7, 10 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 1-7, 10 and 11 recite the broad recitation "unresponsive to bacterial cell components," and the claim also recites "unresponsive to a lipoprotein/lipopeptide" which is the narrower statement of the range/limitation. It is unclear whether the animal is required to be unresponsive to other bacterial cell components besides lipoprotein/lipopeptide.

Regarding claims 1-7, 10 and 11, the term "characterized" renders the claims indefinite because it is unclear what is the characteristics Applicants are referring to. In other words, is the animal unresponsive to the lipoprotein only or other bacterial cell components as well?

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Regarding claim 2, the word “derived” renders the claim indefinite because the nature and number of derivative process is unknown. As such, the metes and bounds of the claims cannot be established.

Regarding claim 6, the word “lopoteichoic” renders the claim indefinite because its meaning is unknown. It appears that the word is mis-spelled. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

This rejection is based on a 102(a) date availability since the foreign priority document has not been perfected. A certified English translation of the foreign priority document would remove the availability of the reference under 102(a) if all the claimed subject matter is disclosed in the foreign priority document.

Claims 1, 3-6, 10 and 11 are rejected under 35 U.S.C. 102(a) as being anticipated by Takeuchi et al. (1999, Immunity, Vol. 11, pp.443-451).

Takeuchi et al. disclose that TLR4 deficient mice are unresponsive to LPS induced shock (see page 445, 1st col., 2nd paragraph, last two lines and Figure 2). Takeuchi et al. also disclose that TLR2 deficient mice are unresponsive to S. aureus peptidoglycan (see page 447, 1st col.,

lines 22-23 and Figure 6A) induced NO₂ production. Takeuchi et al. further disclose that TLR4 deficient mice are unresponsive to lipoteichoic acid isolated from *S. aureus* (see page 447, 1st col., 2nd paragraph, lines 12-14 and Figure 6C). Therefore, Takeuchi et al. disclose the instant claimed invention.

Claims 1, 3-5, 10 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Vacheron et al. (1983, Infection and Immunity, Vol. 42, No. 3, pp. 1049-1054).

Vacheron et al. disclose that murine thymocytes collected from CH3/HeJ mice are not responsive to peptidoglycan stimulation (see page 1051, 2nd paragraph, lines 4-5). Vacheron et al. also disclose that CH3/HeJ mouse macrophages are unresponsive to bacterial endotoxin lipopolysaccharide (see page 1052, 1st col. last line through 2nd col. first line). Therefore, Vacheron et al. disclose the instant claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Anne-Marie Falk
ANNE-MARIE FALK, PH.D.
PRIMARY EXAMINER

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Celine Qian, Ph.D.

January 13, 2003